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EXAMINER	
BABIC, CHRISTOPHER M	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 01/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/693,609	SHORT ET AL.	
	Examiner	Art Unit	
	Christopher M. Babic	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-48,51 and 52* is/are pending in the application.

4a) Of the above claim(s) *49,50,53 and 54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-48,51 and 52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 October 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 2/13/06
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Seq Comp Notice*.

DETAILED ACTION

Election/Restrictions

Applicant's election of Group I, Claims 1-48, 51, and 52, drawn to a method for detecting a nucleic acid in the reply filed on November 7, 2005 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 49, 50, 53, and 54 are withdrawn.

Sequence Rules Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) before the application can be examined under 35 U.S.C. §§ 131 and 132.

Applicant is given time of reply to this office action within which to comply with the sequence rules, 37 C.F.R. §§ 1.821-1.825. Failure to comply with these requirements will result in **abandonment** of the application under 37 C.F.R. § 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension

fee under the provisions of 37 C.F.R. § 1.136. In no case may an applicant extend the period for response beyond the six month statutory period. Direct the response to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the response.

Pages 100 and 116 contain sequences without SEQ ID NOs. If these sequences are included in the sequence listing provide by Applicant, the specification should be amended to include the SEQ ID NOs. If these sequences were not included in the sequence listing filed August 30, 2002. Applicant should provide a substitute sequence listing and a CRF that include those sequences.

Specification

Applicant is reminded of the proper content of an abstract of the disclosure.

A patent abstract is a concise statement of the technical disclosure of the patent and should include that which is new in the art to which the invention pertains. If the patent is of a basic nature, the entire technical disclosure may be new in the art, and the abstract should be directed to the entire disclosure. If the patent is in the nature of an improvement in an old apparatus, process, product, or composition, the abstract should include the technical disclosure of the improvement. In certain patents, particularly those for compounds and compositions, wherein the process for making and/or the use thereof are not obvious, the abstract should set forth a process for making and/or use thereof. If the new technical disclosure involves modifications or alternatives, the abstract should mention by way of example the preferred modification or alternative.

The abstract should not refer to purported merits or speculative applications of the invention and should not compare the invention with the prior art.

Where applicable, the abstract should include the following:
(1) if a machine or apparatus, its organization and operation;
(2) if an article, its method of making;
(3) if a chemical compound, its identity and use;
(4) if a mixture, its ingredients;
(5) if a process, the steps.

Extensive mechanical and design details of apparatus should not be given.

The abstract of the disclosure is objected to because it does not appropriately describe the invention. Correction is required. See MPEP § 608.01(b).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

It is noted that only representative claims will be discussed.

Claims 1-48 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over Claims 1-10 of copending application Aydin (10/666806).

Aydin recites a method for detecting at least one target nucleic acid sequence in a sample comprising: forming a ligation reaction composition comprising the sample and a ligation probe set for each target nucleic acid sequence, the probe set comprising (a) at least one first probe, comprising a target-specific portion and a 5' primer-specific portion, wherein the 5' primer-specific portion comprises a sequence, and (b) at least one second probe, comprising a target-specific portion and a 3' primer-specific portion, wherein the 3' primer-specific portion comprises a sequence, wherein the probes in each set are suitable for ligation together when hybridized adjacent to one another on a complementary target nucleic acid sequence, and wherein one probe in each probe set further comprises an addressable portion located between the primer-specific portion and the target-specific portion, wherein the addressable portion comprises a sequence; forming a test composition by subjecting the ligation reaction composition to at least one cycle of ligation, wherein adjacently hybridizing complementary probes are ligated to one another to form a ligation product comprising the 5' primer-specific portion, the target-specific portions, the addressable portion, and the 3' primer-specific portion; forming an amplification reaction composition comprising: the test composition; a polymerase; a labeled probe, wherein the labeled probe has a first detectable signal value when it is not hybridized to a complementary sequence, and wherein the labeled probe comprises the sequence of the addressable portion or comprises a sequence complementary to the sequence of the addressable portion; and at least one primer set, the primer set comprising (i) at least one first primer comprising the sequence of the 5' primer-specific portion of the ligation product, and (ii) at least one second primer

comprising a sequence complementary to the sequence of the 3' primer-specific portion of the ligation product; subjecting the amplification reaction composition to at least one amplification reaction; and detecting a second detectable signal value at least one of during and after the amplification reaction, wherein a threshold difference between the first detectable signal value and the second detectable signal value indicates the presence of the target nucleic acid sequence, and wherein no threshold difference between the first detectable signal value and the second detectable signal value indicates the absence of the target nucleic acid sequence.

Although the conflicting claims are not identical, they are not patentably distinct from each other because they are both drawn to the same general inventive concept of detecting a target nucleic acid comprising a ligation detection reaction further comprising detecting threshold difference of detectable signals.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. Claims 1-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barany et al. (U.S. 6,027,889) in view of Wittwer et al. (U.S. 6,303,305), in further view of Godfrey et al. "Quantitative mRNA Expression Analysis from Formalin-Fixed, Paraffin-Embedded Tissues Using 5' Nuclease Transcription-Polymerase Chain Reaction" Journal of Molecular Diagnostics. 2000. Vol. 2, No. 2: Pages 84-91).

With regard to Claim 1, Barany et al. discloses a method for detecting the presence or absence of at least one target nucleic acid sequence in a sample (Figures 8-12; Columns 9-11; Columns 23-30; Column 41, Example 4, for example) comprising: forming a ligation reaction composition comprising the sample, and a ligation probe set for each target nucleic acid sequence, the probe set comprising (a) at least one first probe, comprising a target-specific portion and a 5' primer-specific portion, wherein the 5' primer-specific portion comprises a sequence, and (b) at least one second probe, comprising a target-specific portion and a 3' primer-specific portion, wherein the 3' primer-specific portion comprises a sequence, wherein the probes in each set are suitable for ligation together when hybridized adjacent to one another on a complementary target sequence; forming a test composition by subjecting the ligation reaction composition to at least one cycle of ligation, wherein adjacently hybridizing complementary probes are ligated to one another to form a ligation product comprising the 5' primer-specific portion, the target-specific portions, and the 3' primer-specific portion

Barany et al. disclose a subsequent amplification step with labeled primers (Figure 11,12; Columns 24,25, for example), however, does not expressly disclose employing real-time detection methods using double stranded dependent labels, or detection through comparing threshold values.

Wittwer et al. discloses methods for nucleic acid detection comprising determining threshold cycle values (C_t) (Column 3, Lines 16-51, for example) and threshold time values (T_t) (Column 2, Lines 38-45, for example) with double stranded dependent labels (Column 10, Example 2, for example). Wittwer et al. does not expressly disclose the comparison of threshold values.

Godfrey et al. disclose methods for comparing real-time detection values (Abstract; Page 86, Column 2; Page 87, Column 1). They expressly disclose detecting differences in threshold values to quantify the amount of PCR target (Page 86, Column 1, for example).

Based on the combined disclosures of the applied references, it would have been obvious to one of ordinary skill in the art at the time of invention to modify the ligation dependent reaction/amplification (i.e. LDR/PCR) methods of Barany et al. to incorporate real-time detection methods using double-stranded dependent labels. It would have been further obvious to one of ordinary skill in the art at the time of invention to detect the presence of a particular nucleic acid sample by comparing threshold values based on signals from double-stranded dependent labels. A practitioner of ordinary skill in the art would have recognized that if a particular probe set failed to ligate due to a particular nucleotide mismatch (i.e. SNP or allele), it would fail to produce a threshold value in

subsequent amplification reactions (and vice versa) thereby allowing one to determine a particular allele at a given locus (i.e. heterozygosity or homozygosity) by comparison of threshold values. At the time of invention, the disclosure of Wittwer et al. and Godfrey et al. clearly would have provided the instruction and motivation necessary for one of ordinary skill in the art to practice the methods as claimed. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of invention to practice the instant methods as claimed.

With regard to Claims 2-5, Barany et al. disclose identifying one or more of a plurality of sequences, differing by one or more single-base, in a plurality of target nucleotide sequences (Column 23, Lines 10-20, for example). They further disclose one or more oligonucleotide probe sets (Column 23, Lines 15-35, for example). They further disclose one or a plurality of oligonucleotide primer sets (Column 23, Lines 25-30, for example).

With regard to Claim 6, Barany et al. disclose identifying one or more of a plurality of sequences, differing by one or more single-base, in a plurality of target nucleotide sequences (Column 23, Lines 10-20, for example).

With regard to Claim 7, Barany et al. disclose a method for detecting the presence or absence of at least one target nucleic acid sequence in a sample (Figures 8-12; Columns 9-11; Columns 23-30; Column 41, Example 4, for example) comprising: forming a ligation reaction composition comprising the sample, and a ligation probe set for each target nucleic acid sequence, the probe set comprising (a) at least one first probe, comprising a target-specific portion and a 5' primer-specific portion, wherein the

5' primer-specific portion comprises a sequence, and (b) at least one second probe, comprising a target-specific portion and a 3' primer-specific portion, wherein the 3' primer-specific portion comprises a sequence, wherein the probes in each set are suitable for ligation together when hybridized adjacent to one another on a complementary target sequence; forming a test composition by subjecting the ligation reaction composition to at least one cycle of ligation, wherein adjacently hybridizing complementary probes are ligated to one another to form a ligation product comprising the 5' primer-specific portion, the target-specific portions, and the 3' primer-specific portion; forming at least one amplification reaction composition comprising: at least a portion of the test composition, a polymerase, a double-stranded-dependent label; and at least one primer set, the primer set comprising (i) at least one first primer comprising the sequence of the 5' primer-specific portion of the ligation product, and (ii) at least one second primer comprising a sequence complementary to the sequence of the 3' primer-specific portion of the ligation product.

Barany et al. disclose a subsequent amplification step with labeled primers (Figure 11,12; Columns 24,25, for example), however, does not expressly disclose employing real-time detection methods using double stranded dependent labels, or detection through comparing threshold values.

Wittwer et al. discloses methods for nucleic acid detection comprising determining threshold cycle values (C_t) (Column 3, Lines 16-51, for example) and threshold time values (T_t) (Column 2, Lines 38-45, for example) with double stranded

dependent labels (Column 10, Example 2, for example). Wittwer et al. does not expressly disclose the comparison of threshold values.

Godfrey et al. disclose methods for comparing real-time detection values (Abstract; Page 86, Column 2; Page 87, Column 1). They expressly disclose detecting differences in threshold values to quantify the amount of PCR target (Page 86, Column 1, for example).

Based on the combined disclosures of the applied references, it would have obvious to one of ordinary skill in the art at the time of invention to modify the ligation dependent reaction/amplification (i.e. LDR/PCR) methods of Barany et al. to incorporate real-time detection methods using double-stranded dependent labels. It would have been further obvious to one of ordinary skill in the art at the time of invention to detect the presence of a particular nucleic acid sample by comparing threshold values based on signals from double-stranded dependent labels. A practitioner of ordinary skill in the art would have recognized that if a particular probe set failed to ligate due to a particular nucleotide mismatch (i.e. SNP or allele), it would fail to produce a threshold value in subsequent amplification reactions (and vice versa) thereby allowing one to determine a particular allele at a given locus (i.e. heterozygosity or homozygosity) by comparison of threshold values. At the time of invention, the disclosure of Wittwer et al. and Godfrey et al. clearly would have provided the instruction and motivation necessary for one of ordinary skill in the art to practice the methods as claimed. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of invention to practice the instant methods as claimed.

With regard to Claims 8 and 9, Wittwer et al. discloses methods for nucleic acid detection comprising determining threshold cycle values (C_t) (Column 3, Lines 16-51, for example) and threshold time values (T_t) (Column 2, Lines 38-45, for example) with double stranded dependent labels (Column 10, Example 2, for example).

With regard to Claims 10, 11, 18, and 19, Barany et al. disclose identifying one or more of a plurality of sequences, differing by one or more single-base, in a plurality of target nucleotide sequences (Column 23, Lines 10-20, for example). They further disclose one or more oligonucleotide probe sets (Column 23, Lines 15-35, for example). They further disclose one or a plurality of oligonucleotide primer sets (Column 23, Lines 25-30, for example).

With regard to Claims 8, 12, 13, 14, and 19-22, Wittwer et al. discloses methods for nucleic acid detection comprising determining threshold cycle values (C_t) (Column 3, Lines 16-51, for example). Wittwer et al. does not expressly disclose the comparison of threshold values.

Godfrey et al. disclose methods for comparing real-time detection values (Abstract; Page 86, Column 2; Page 87, Column 1). They expressly disclose detecting differences in threshold values to quantify the amount of PCR target (Page 86, Column 1, for example).

Based on the combined disclosures of the applied references, it would have obvious to one of ordinary skill in the art at the time of invention to modify the ligation dependent reaction/amplification (i.e. LDR/PCR) methods of Barany et al. to incorporate real-time detection methods using double-stranded dependent labels. It would have

been further obvious to one of ordinary skill in the art at the time of invention to detect the presence of a particular nucleic acid sample by comparing threshold values based on signals from double-stranded dependent labels. A practitioner of ordinary skill in the art would have recognized that if a particular probe set failed to ligate due to a particular nucleotide mismatch (i.e. SNP or allele), it would fail to produce a threshold value in subsequent amplification reactions (and vice versa) thereby allowing one to determine a particular allele at a given locus (i.e. heterozygosity or homozygosity) by comparison of threshold values. At the time of invention, the disclosure of Wittwer et al. and Godfrey et al. clearly would have provided the instruction and motivation necessary for one of ordinary skill in the art to practice the methods as claimed. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of invention to practice the instant methods as claimed.

With regard to Claims 9, 15, 16, 17, and 23-25, Wittwer et al. discloses methods for nucleic acid detection comprising determining threshold time values (T_t) (Column 2, Lines 38-45, for example). Wittwer et al. does not expressly disclose the comparison of threshold values.

Godfrey et al. disclose methods for comparing real-time detection values (Abstract; Page 86, Column 2; Page 87, Column 1). They expressly disclose detecting differences in threshold values to quantify the amount of PCR target (Page 86, Column 1, for example). Godfrey et al. do not expressly disclose comparison of threshold time values (T_t), however, it would have been obvious to one of ordinary skill in the art that the comparison of any threshold value, whether as a function amplification time or cycle,

would have yielded identical results. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of invention to practice the instant methods as claimed.

With regard to Claim 26, Barany et al. disclose a method for detecting the presence or absence of at least one target nucleic acid sequence in a sample (Figures 8-12; Columns 9-11; Columns 23-30; Column 41, Example 4, for example) comprising: (a) forming at least one reaction composition comprising: the sample; a ligation probe set for the target nucleic acid sequence, the probe set comprising (a) at least one first probe, comprising a target-specific portion and a 5' primer-specific portion, wherein the 5' primer-specific portion comprises a sequence and (b) at least one second probe, comprising a target-specific portion and a 3' primer-specific portion, wherein the 3' primer-specific portion comprises a sequence, wherein the probes in each set are suitable for ligation together when hybridized adjacent to one another on a complementary target sequence; a polymerase; a double-stranded-dependent label, wherein the double-stranded-dependent label has a first detectable signal value when the double-stranded-dependent label is not exposed to double-stranded nucleic acid; and at least one primer set, the primer set comprising (i) at least one first primer comprising the sequence of the 5' primer-specific portion of the ligation product, and (ii) at least one second primer comprising a sequence complementary to the sequence of the 3' primer-specific portion of the ligation product; (b) subjecting the reaction composition to at least one cycle of ligation, wherein adjacently hybridizing complementary probes are ligated to one another to form a ligation product comprising

the 5' primer-specific portion, the target-specific portions, and the 3' primer-specific portion.

Barany et al. disclose a subsequent amplification step with labeled primers (Figure 11,12; Columns 24,25, for example), however, does not expressly disclose employing real-time detection methods using double stranded dependent labels, or detection through comparing threshold values.

Wittwer et al. discloses methods for nucleic acid detection comprising determining threshold cycle values (C_t) (Column 3, Lines 16-51, for example) and threshold time values (T_t) (Column 2, Lines 38-45, for example) with double stranded dependent labels (Column 10, Example 2, for example). Wittwer et al. does not expressly disclose the comparison of threshold values.

Godfrey et al. disclose methods for comparing real-time detection values (Abstract; Page 86, Column 2; Page 87, Column 1). They expressly disclose detecting differences in threshold values to quantify the amount of PCR target (Page 86, Column 1, for example).

Based on the combined disclosures of the applied references, it would have obvious to one of ordinary skill in the art at the time of invention to modify the ligation dependent reaction/amplification (i.e. LDR/PCR) methods of Barany et al. to incorporate real-time detection methods using double-stranded dependent labels. It would have been further obvious to one of ordinary skill in the art at the time of invention to detect the presence of a particular nucleic acid sample by comparing threshold values based on signals from double-stranded dependent labels. A practitioner of ordinary skill in the

art would have recognized that if a particular probe set failed to ligate due to a particular nucleotide mismatch (i.e. SNP or allele), it would fail to produce a threshold value in subsequent amplification reactions (and vice versa) thereby allowing one to determine a particular allele at a given locus (i.e. heterozygosity or homozygosity) by comparison of threshold values. At the time of invention, the disclosure of Wittwer et al. and Godfrey et al. clearly would have provided the instruction and motivation necessary for one of ordinary skill in the art to practice the methods as claimed. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of invention to practice the instant methods as claimed.

With regard to Claims 29-31, Barany et al. disclose identifying one or more of a plurality of sequences, differing by one or more single-base, in a plurality of target nucleotide sequences (Column 23, Lines 10-20, for example). They further disclose one or more oligonucleotide probe sets (Column 23, Lines 15-35, for example). They further disclose one or a plurality of oligonucleotide primer sets (Column 23, Lines 25-30, for example).

With regard to Claim 32, please refer to the rejection of Claim 6 above.

With regard to Claim 33, Barany et al. disclose a method for detecting the presence or absence of at least one target nucleic acid sequence in a sample (Figures 8-12; Columns 9-11; Columns 23-30; Column 41, Example 4, for example) comprising: (a) forming at least one reaction composition comprising: the sample; a ligation probe set for the target nucleic acid sequence, the probe set comprising (a) at least one first probe, comprising a target-specific portion and a 5' primer-specific portion, wherein the

5' primer-specific portion comprises a sequence and (b) at least one second probe, comprising a target-specific portion and a 3' primer-specific portion, wherein the 3' primer-specific portion comprises a sequence, wherein the probes in each set are suitable for ligation together when hybridized adjacent to one another on a complementary target sequence; a polymerase; a double-stranded-dependent label; and at least one primer set, the primer set comprising (i) at least one first primer comprising the sequence of the 5' primer-specific portion of the ligation product, and (ii) at least one second primer comprising a sequence complementary to the sequence of the 3' primer-specific portion of the ligation product; (b) subjecting the reaction composition to at least one cycle of ligation, wherein adjacently hybridizing complementary probes are ligated to one another to form a ligation product comprising the 5' primer-specific portion, the target-specific portions, and the 3' primer-specific portion

Barany et al. disclose a subsequent amplification step with labeled primers (Figure 11,12; Columns 24,25, for example), however, does not expressly disclose employing real-time detection methods using double stranded dependent labels, or detection through comparing threshold values.

Wittwer et al. discloses methods for nucleic acid detection comprising determining threshold cycle values (C_t) (Column 3, Lines 16-51, for example) and threshold time values (T_t) (Column 2, Lines 38-45, for example) with double stranded dependent labels (Column 10, Example 2, for example). Wittwer et al. does not expressly disclose the comparison of threshold values.

Godfrey et al. disclose methods for comparing real-time detection values (Abstract; Page 86, Column 2; Page 87, Column 1). They expressly disclose detecting differences in threshold values to quantify the amount of PCR target (Page 86, Column 1, for example).

Based on the combined disclosures of the applied references, it would have obvious to one of ordinary skill in the art at the time of invention to modify the ligation dependent reaction/amplification (i.e. LDR/PCR) methods of Barany et al. to incorporate real-time detection methods using double-stranded dependent labels. It would have been further obvious to one of ordinary skill in the art at the time of invention to detect the presence of a particular nucleic acid sample by comparing threshold values based on signals from double-stranded dependent labels. A practitioner of ordinary skill in the art would have recognized that if a particular probe set failed to ligate due to a particular nucleotide mismatch (i.e. SNP or allele), it would fail to produce a threshold value in subsequent amplification reactions (and vice versa) thereby allowing one to determine a particular allele at a given locus (i.e. heterozygosity or homozygosity) by comparison of threshold values. At the time of invention, the disclosure of Wittwer et al. and Godfrey et al. clearly would have provided the instruction and motivation necessary for one of ordinary skill in the art to practice the methods as claimed. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of invention to practice the instant methods as claimed.

With regard to Claim 34 and 35, please refer to the rejection of Claims 8 and 9 above.

With regard to Claim 36, please refer to the rejection of Claims 2-5 above.

With regard to Claim 37, 40, and 41, please refer to the rejection of Claims 8, 12, 13, 14, and 19-22 above.

With regard to Claim 38 and 39, please refer to the rejection of Claim 6 above.

With regard to Claim 42, 44, and 45, please refer to the rejections of Claims 9, 15, 16, 17, and 23-25 above.

With regard to Claim 42, please refer to the rejection of Claim 6 above.

With regard to Claims 46-48, please refer to the rejection of Claims 2-5 above.

2. Claims 51 and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barany et al. (U.S. 6,027,889) in view of Barany et al. (U.S. 6,312,892).

The methods of Barany et al. ('889) have been outlined in the above rejections. Barany et al. ('889) do not expressly disclose the incorporation of nucleotide analogues.

Barany et al. ('892) discloses the above LDR/PCR methods with the use of nucleotide analogues (Figure 9; Column 33, Line 45-Column 34, Line 25, for example). They expressly disclose use of a nucleotide analogue to reduce the amount ligation formed off minority mutant targets, and thus, not overwhelming the signal (Column 34, Lines 1-25, for example). Barany et al. ('892) does not expressly disclose the use of poly-deoxy-inosinic-deoxy-cytidylic acid, however, they disclose several representative nucleotide analogues, including inosine-based analogues.

Based on the combined disclosures of the applied references, it would have been obvious to one of ordinary skill in the art to modify the LDR/PCR methods of Barany et al. to incorporate nucleotide analogues such as poly-deoxy-inosinic-deoxy-cytidylic acid. The motivation to do so, provided by Barany et al. ('892), would have been to reduce the amount ligation formed off minority mutant targets. At the time of invention, the disclosure of Barany et al. ('892) clearly would have provided the instruction necessary for one of ordinary skill in the art to practice the methods as claimed. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of invention to practice the instant methods as claimed.

Conclusion

Claims 1-48, 51, and 52 are rejected. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher M. Babic whose telephone number is 571-272-8507. The examiner can normally be reached on Monday-Friday 7:00AM to 4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

11/9/05

Christopher M. Babic
Patent Examiner
AU 1637

KENNETH R. HORLICK, PH.D
PRIMARY EXAMINER

1/9/06

Notice to Comply	Application No. 10/693609	Applicant(s) Shortet al.
	Examiner Christopher M. Babic	Art Unit 1637

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1; 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: See Office Action

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

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